REMARKS

Summary of the Office Action

Prior to entry of the present amendment, claims 1-3 and 22-34 are pending in the application. Claims 4-21 were previously canceled. Claims 1-3 and 22-34 are rejected under 35 U.S.C. § 112, first paragraph and under 35 U.S.C. § 112, second paragraph. Applicants address each basis for rejection as follows.

Priority

The Office asserts that claims 22 and 32 are not entitled to the priority date of Provisional Application Serial No. 60/410,610 ("the '610 application), as this application does not provide support for the genes *lin-15A* and *lin-38*. Applicants respectfully disagree.

Applicants submit that claims 22 and 32 are entitled, under 35 U.S.C. § 119(e), to benefit of the filing date of Provisional Application Serial No. 60/410,610 filed September 12, 2002. The '610 application, at page 16, third paragraph, describes *lin-15A* and *lin-38* as Class A synthetic multivulval genes. As such, the disclosure of the '610 application provides support for claims 22 and 32 that meets the requirements of 35 U.S.C. § 112, first paragraph, and claims 22 and 32 are entitled to benefit of the September 12, 2002 filing date of the '610 application.

Summary of the Invention

Applicants have discovered new members of the synMuv gene family. Applicants provide methods for the identification of candidate compounds that may be used to treat a neoplasia. The methods require detecting cell proliferation in a cell having a loss of function mutation in a Class B synMuv gene: *mep-1*, *lin(n3628)*, *lin(n4256)*, or *lin-65*; and a second loss of function mutation in a Class A synMuv gene following exposure of the cell to a candidate compound, and comparing the cell proliferation to a control cell. A

decrease in cell proliferation relative to the control cell identifies the compound as being a candidate compound for treating a neoplasia.

Amendments to the Claims

Claims 1, 23, 27, and 31 have been amended to specify that the requirement for a nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 24, 26, 28, or 2, respectively, *includes* the loss of function mutation.

No new matter has been added by the present amendment. Applicants reserve the right to pursue any canceled subject matter in this or in a continuing application.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 1-3 and 22-34 are rejected under 35 U.S.C. § 112, first paragraph for lack of enablement. As the basis for this rejection, the Office states "the breadth of the more limiting claims which read on *any* cell in a nematode or any type of an isolated mammalian cell, would still be too broad to ensure the same outcome...obtained using synMuv mutants in the precursor vulval tissue of *C. elegans*" (Office Action, pp. 7-8; emphasis original); the specification "does not provide direction or evidence of working examples to establish whether the invention is enabled for all cell types, all cells in a nematode, or all types of isolated mammalian cells" (Office Action, pg. 9); and "undue experimentation with various cell types [is required] to determine whether the assay would be able to identify candidate compounds for treating neoplasia" (Office Action, pg. 9). Applicants respectfully disagree.

Applicants submit that given (1) the Examples in the specification and (2) the high degree of structural and functional homology between members of the synthetic multivulval signaling pathway and the members of the Ras-signaling and Rb-signaling pathways; a skilled artisan in the field of molecular biology could use the method of

amended claims 1, 23, 27, and 31 in a variety of cells (e.g., additional nematode cell types and mammalian cell types).

As the Office has noted above, the specification teaches the use of precursor vulval tissue in the method of amended claims 1, 23, 27, and 31. In addition to the teachings of the specification, Applicants submit that, at the time of filing of the present application, Ras family genes and Rb family genes were known to be structurally and functionally conserved between *C. elegans* and mammals, and expressed in a variety of cell types. On this point, Applicants direct the Office's attention to the disclosed Declaration by Dr. H. Robert Horvitz. Dr. Horvitz states (paragraph 2):

> Prior to the filing date of the application, Ras family genes and Rb family genes were known to be structurally and functionally conserved between *C. elegans* and mammals, and expressed in a variety of cell types. Based on the known conservation of Ras family and Rb family genes in numerous cell types, and the Examples in the specification of the present application, I would have expected, at the time of filing, one skilled in the art of molecular biology to have been capable of using the methods claimed in the present application that utilize a cell having a loss of function mutation in *mep-1*, *lin(n3628)*, *lin(n4256)*, or *lin-65*, and a second loss of function in a Class A synMuv gene, to identify candidate compounds for treating neoplasia using any one of a variety of cell types including various *C. elegans* and mammalian cells.

Moreover, the specification teaches that Class A synMuv and Class B synMuv genes are structurally and functionally homologous to members of the Ras- and Rb-signaling pathways, respectively. Accordingly, based on the known conservation of Ras family and Rb family genes, and the Examples in the specification of the present application, Applicants submit that one skilled in the art of molecular biology could use, without undue experimentation, the methods claimed in the present application that utilize a cell having a loss of function mutation in *mep-1*, *lin(n3628)*, *lin(n4256)*, or *lin-65*, and a second loss of function in a Class A synMuv gene, in a variety of cell types (for example, other *C. elegans* or mammalian cells).

With regard to the knowledge in the art concerning the conservation of Ras family and Rb family genes, Applicants direct the Office's attention to Santos and Nebreda (*FASEB J.* 3:2151-2163, 1989; submitted with the Reply to Office Action filed October 30, 2007; "Santos") and Saito et al. (*Cancer Invest.* 20:264-275, 2002; Exhibit B). In particular, Santos states:

> Ras genes appear to be ubiquitous in eukaryotic cells, and yeasts are the lowest organisms found to possess functional ras genes. The remarkable degree of conservation between species as far apart in evolution as yeast and human strongly suggests that ras gene products play a fundamental role in key cellular processes. (Pg. 2152, left column, second paragraph).

and Saito et al. states:

> Many other [*C. elegans*] genes have been found to regulate the ras signal-transduction pathway....[I]t is important to mention that several of these genes are presently novel but will likely have *mammalian counterparts*. (Pg. 270; emphasis added).

Regarding the conservation of members of the Rb gene family, the specification states (page 1, lines 19-28):

> Retinoblastoma (Rb) family proteins are mammalian tumor suppressors that regulate cell proliferation. This pathway is conserved among a variety of species, including the nematode, *Caenorhabditis elegans*. (Emphasis added).

Clearly, the Ras-signaling and Rb-signaling families are highly conserved. As such, Applicants submit that one skilled in the art would be able to use the methods of the amended claims in a variety of cell types without undue experimentation. This basis for rejection should be withdrawn.

As a further basis of rejection, the Office states that "the prior art teaches that use of isolated mammalian cells are not predictable models of cancer" (Office Action, pg. 9) and that "more work will be necessary to ... provide a precise picture of how these

processes relate to one another" (Office Action, pg. 8). Applicants respectfully disagree with this basis for rejection.

The amended claims are directed to an *in vitro* method of identifying *candidate* compounds useful for the treatment of a neoplasia. These are *candidate* compounds. The amended claims are not directed to an *animal model of cancer*. Applicants submit that, at the time of filing, *in vitro* screening assays of candidate compounds using cells were standard in the art. Applicants further submit that, at the time of filing, cell culture models of cancer were known to share many aspects of cancer (e.g., unregulated cell proliferation).

The presently claimed methods are used to identify *candidate* compounds. Clearly, such candidate compounds will require further testing in animal models of cancer to verify their therapeutic potential *in vivo*. There can be no question that the specification enables screening methods to identify candidate compounds. This basis for rejection should be withdrawn.

Applicants further submit that 35 U.S.C. § 112, first paragraph, does not require that the specification disclose the mechanism of action of a particular compound identified using the claimed methods. Enablement simply requires that the specification, in combination with the knowledge in the art, teaches the skilled artisan how to make and use the claimed invention. For the above reasons, Applicants submit that the specification meets the enablement requirement for claims 1-3 and 22-34. This basis for rejection should also be withdrawn.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 1-3 and 22-34 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite. As the basis for the rejection, the Office states that "it is unclear whether the requirement for at least 95% sequence identity to the respective sequences of SEQ ID NOS: 24, 26, 28, and 2, is for a sequence which *includes* the 'loss of function'

mutation *in addition* to the requirement for a 95% sequence identity to the SEQ ID NOS" (Office Action, pg. 10; emphasis original).

As described above, Applicants have amended claims 1, 23, 27, and 31 to specify that the limitation for at least 95% sequence identity to SEQ ID NO: 24, 26, 28, or 2, respectively, *includes* the loss of function mutation. Applicants submit that the sequence of SEQ ID NOS: 24, 26, 28, and 2 are the wildtype sequences and, therefore, the limitation of 95% sequence identity to SEQ ID NO: 24, 26, 28, or 2 includes the loss of function mutation. This rejection may now be withdrawn.

CONCLUSION

Applicants submit that the application is in condition for allowance and such action is hereby requested.

Enclosed is a Request for Continued Examination; a Petition to extend the period for replying to the final Office Action for three months, to and including August 7, 2008, and a check in payment of the required extension fee.

If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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